

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

DO

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|----|---|
| (51) International Patent Classification 5 : A61L 27/00 | A1 | (11) International Publication Number: WO 93/09819 (43) International Publication Date: 27 May 1993 (27.05.93) |
| (21) International Application Number: PCT/GB92/02128 (22) International Filing Date: 17 November 1992 (17.11.92) | | (74) Agent: EYLES, Winifred, Joyce; Patents Department, British Technology Group Ltd., 101 Newington Causeway, London SE1 6BU (GB). |
| (30) Priority data: 9124487.1 18 November 1991 (18.11.91) GB | | (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). |
| (71)(72) Applicants and Inventors: BRADEN, Michael [GB/GB]; 68 Cravells Road, Harpenden, Herts AL5 1BD (GB). DOWNES, Sandra [GB/GB]; 74 Mill Way, Bushley, Watford, Herts WD2 2AG (GB). PATEL, Mangala, Prakesh [GB/GB]; 45 Ellesmere Avenue, Mill Hill, London NW7 3EX (GB). DAVY, Kenneth, Walter, Michael [GB/GB]; 11 Chapel Gardens, Lindford, Nr Bordon, Hampshire GU35 0TA (GB). | | Published <i>With international search report.</i> |

(54) Title: THE USE OF BIOMATERIALS FOR TISSUE REPAIR

(57) Abstract

A curable composition of a monomeric heterocyclic acrylic or methacrylic ester and an acrylate or methacrylate polymer is used to promote tissue repair, especially cartilage repair.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|--|----|--------------------------|
| AT | Austria | FR | France | MR | Mauritania |
| AU | Australia | GA | Gabon | MW | Malawi |
| BB | Barbados | GB | United Kingdom | NL | Netherlands |
| BE | Belgium | GN | Guinea | NO | Norway |
| BF | Burkina Faso | GR | Greece | NZ | New Zealand |
| BG | Bulgaria | HU | Hungary | PL | Poland |
| BJ | Benin | IE | Ireland | PT | Portugal |
| BR | Brazil | IT | Italy | RO | Romania |
| CA | Canada | JP | Japan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SK | Slovak Republic |
| CI | Côte d'Ivoire | LJ | Liechtenstein | SN | Senegal |
| CM | Cameroon | LK | Sri Lanka | SU | Soviet Union |
| CS | Czechoslovakia | LU | Luxembourg | TD | Chad |
| CZ | Czech Republic | MC | Monaco | TG | Togo |
| DE | Germany | MG | Madagascar | UA | Ukraine |
| DK | Denmark | ML | Mali | US | United States of America |
| ES | Spain | MN | Mongolia | VN | Viet Nam |

THE USE OF BIOMATERIALS FOR TISSUE REPAIR

This invention relates to the use of biomaterials for tissue repair and is particularly concerned with the use of 5 physiologically acceptable polymeric materials in such tissue repair, especially cartilage repair.

The use of physiologically acceptable polymeric materials in the preparation of biomedical appliances such as hearing aids, artificial eyes and dentures is well known, as is the use of 10 polymeric materials as bone cements in the field of orthopaedics. Such polymeric materials are often used in the form of a curable composition which is initially in a fluid, semi-liquid, dough-like or other mouldable form, but which cures or hardens at the temperature of use to form a strong solid of physical properties 15 dependent on the use to which it is being put. Examples of such curable compositions are to be found in International Patent Application No. WO89/03695 and GB Patent 2 107 341 which disclose the use of curable compositions comprising a powdered methacrylate polymer mixed with a methacrylate monomer. For such applications 20 as the preparation of hearing aids, artificial eyes and dentures which require dimensional accuracy, it is important to provide compositions of low linear curing shrinkage and GB Patent 2 107 341 is directed to such an aim. For use as bone cement it is important to prevent subsequent failure at the bone-cement 25 interface and, to this end, WO89/03695 discloses the inclusion of a cell growth stimulant such as human growth hormone so as to increase the rate of healing of, for example, a bone fracture and give a joint of increased strength. The emphasis in the previous use of these curable compositions has therefore been directed to 30 attaining bonding strength and/or material strength and dimensional stability dependent on the intended use.

- 2 -

Surprisingly, it has been found that certain curable compositions comprising a methacrylate polymer mixed with a suitable unsaturated monomer can be employed to promote tissue repair, with or without the addition of cell growth stimulants such as human growth hormone. Even more surprisingly, it has been found that such compositions can be employed to promote cartilage repair.

Cartilage, which differs from bone in construction, has previously been considered substantially non-repairable. Attempts to repair cartilage currently include the introduction of carbon fibres behind the cartilage; however such carbon fibres are brittle and, while a fibrous tissue forms in the implanted area, the resulting growth is not that of true cartilage composed of chondrocytes expressing their normal phenotype and producing their own matrix components. Implantation of cartilage components and hydrogel compositions have also been tried with limited success. There is therefore a great need for a breakthrough in the treatment of cartilage defects.

According to the present invention there is provided a monomer/polymer mixture for use in the preparation of a curable composition for introduction to a site requiring tissue repair in a human or animal body in order to promote said tissue repair, the monomer component being selected from monomeric esters of general formula I

25



30 wherein R is a hydrogen atom or a methyl group, m is 0, 1 or 2, and X is a 3 to 6 membered heterocyclic ring and the polymer component is selected from acrylate and methacrylate polymers and copolymers thereof. Preferably X is an oxygen containing heterocycle.

35 According to a further aspect of the invention there is provided a process for the promotion of tissue repair

- 3 -

comprising introducing to a site requiring tissue repair in a human or animal body, a curable composition comprising a monomer component selected from monomeric esters of general formula I above and a polymer component selected from acrylate and methacrylate polymers and copolymers thereof and causing or allowing the composition to cure in contact with the site.

The monomeric ester component is preferably selected from methacrylates where X is a heterocyclic group of formula

O

10 / \

$-\text{CH}(\text{R})\text{--}(\text{CH}_2)_n$ where n is 1, 2, 3 or 4. Tetrahydrofurfuryl

methacrylate ($\text{R}=\text{CH}_3$, m=1, n=3) is particularly preferred.

These monomers may be admixed with other monomers to control hydrophilicity, for example hydroxyethyl methacrylate to

15 increase hydrophilicity or isobornyl methacrylate to decrease hydrophilicity. The polymer component is preferably a

methacrylate polymer, preferably poly(ethyl methacrylate), but other polymers such as poly(methyl methacrylate), poly-

(hydroxyethyl methacrylate), or poly(tetrahydrofurfuryl

20 methacrylate) may be employed as well as copolymers thereof.

The copolymer component may be selected to control hydrophilicity.

The composition is suitably in the form of a mixture of finely divided solid polymer, suitably prepared by suspension

25 polymerisation, in liquid monomer. The composition may include initially, or have added to it at the point of use, suitable

activators for the curing such as free radical catalysts, e.g. peroxide/amine initiator systems. Alternatively,

photoinitiators could be used, e.g. camphor quinone/tertiary

30 amine systems well known in the art. Additional additives such as stabilisers and fillers and x-ray opacifying agents may be present. These include, for example, quinone type inhibitors

in the monomer, and/or inorganic fillers to increase hardness and reduce polymerisation shrinkage. In particular,

35 hydroxyapatite may be used for this purpose and to improve

- 4 -

biocompatibility. In addition, antibiotic components such as gentamicin may be added in order to avoid infection. Other possible therapeutic additives include anti inflammatory drugs, hydrocortisones, dexamethasone and drugs for the treatment of 5 osteoarthritis when promoting tissue repair in a diseased joint. Other examples are antifungal agents and antimicrobial agents. Other possible additives include porosogens such as collagen or dextran to increase the porosity of the material or materials which function as protein carriers.

10 A particularly preferred additive is a cell growth stimulant such as those described in WO89/03695, and in particular, human growth hormone. Other growth factors such as TGF- τ , IGF I, IGF- τ , FDGF and FGF may be used.

15 The ratio of monomer to polymer component can vary dependent on the reaction time required and the consistency of composition required initially. Suitably the ratio of polymer to monomer is from 1:1 to 2:1 by weight, preferably 1.25:1 to 1.75:1. The curing should desirably occur at body temperature and curing is desirably effected over a period of 5 to 20 20 minutes, preferably 10 to 15 minutes. The use of such compositions as biomaterials in dental, aural and ophthalmic fields is described in GB 2 107 341.

25 It is postulated that the ability of such cured compositions to promote tissue repair results from their ability to absorb water to an extent which allows absorption of tissue fluid from the area requiring repair, while swelling in the tissue to provide good bonding conditions. It is postulated that, in order to be well suited for use in accordance with the present invention, the biopolymer 30 composition when cured should have a water uptake in the region of 5 to 30% w/w over a period of six months to 2 years. It is also recognised that the low shrinkage properties of such biopolymers combined with the slight swelling occurring with water uptake give materials which bond firmly in use, for 35 example in cartilage, and are not readily dislodged.

- 5 -

The monomer/polymer mixture of the invention is preferably used to manufacture a composition intended for introduction at, or adjacent to damaged cartilage to promote cartilage repair. It has been found advantageous to apply the composition below, 5 preferably slightly below the surface of the subchondral bone in order to optimize the formation of a new cartilage layer. However, the repair of other damaged tissue such as bone, epithelial and endothelial tissue is also contemplated within the scope of the invention, as a result of enhanced cell 10 proliferation and differentiation in a biologically advantageous matrix.

The invention will now be further described by way of example.

Example 1

15 A curable monomer/polymer composition was prepared by mixing poly(ethyl methacrylate) in powdered form (obtained from Bonar Polymers Ltd., Ref. T/S 1249/4, Newton Aycliffe, Co. Durham, U.K. and of molecular weight about 250,000) (10g) with tetrahydro-furfuryl methacrylate monomer (obtained from Rohm 20 Chemie, Darmstadt, Germany) (5 ml) containing 2.5% v/v of N,N'-dimethyl-p-toluidene as activator. The polymer component contained 8% w/w BaSO₄ incorporated during the polymerisation process to confer radioopacity.

Human growth hormone (obtained from Novo Nordisk, Denmark) 25 was incorporated into the material by mixing 12 IU with 10g powder component prior to adding the monomer.

The composition was cast in discs of diameter 2mm at a temperature of 37°C. Elution of the growth hormone was monitored by immersion of the discs in 0.1M phosphate buffered 30 saline at 37°C at suitable time intervals using a specific ELISA. Figure 1 shows the in vitro release of human growth hormone.

The surface properties of the discs as cast were examined by scanning electron microscopy. This revealed that the cured

- 6 -

polymer had a smooth surface, as compared to the rough surfaces obtained with more conventionally employed polymethyl methacrylate.

Portions of 2ml of the curable composition prepared as above, immediately after mixing, were inserted by syringe into drilled holes in the knees of three rabbits (adult Sandy Lop, weight of least 3.5kg) which were then kept unrestrained for eight months. Rapid healing and wound closure were noted and the rabbits quickly regained mobility and appetite. The tissue response at the bone-polymer interface and cartilage-polymer interface were examined. At the macroscopic level it was apparent that the cartilage defect had healed.

Example 2

A curable composition as described in Example 1 was employed. The composition was in the form of a liquid monomer containing the dispersed polymer.

A single 3 mm diameter defect was drilled into the intercondylar notch of the articular cartilage of 18 mature Sandy Lop rabbits. Into each defect was inserted 0.15 ml of the curable composition containing human growth hormone (12 international units per 5g polymer powder) into the subchondral bone below the area of removed cartilage. Plain curable composition without any growth hormone was inserted into a similar cartilage defect in the contralateral limb. Rabbits were sacrificed at 3, 6, 9 and 12 weeks and 8 months.

Histology. At each time interval, excess bone was removed from the femoral condyles before fixation in 2% paraformaldehyde and 0.5% glutaraldehyde, at 4°C, for 48 hours. Each specimen was decalcified in neutral EDTA at 4°C prior to either low temperature (4°C) dehydration and wax embedding, or frozen section preparation.

Cryosectioning. At each time interval decalcified specimens were frozen in cryomountant using liquid nitrogen. These were cryostat sectioned at -20°C, whilst the polymer was held in place with double-sided sellotape, sections were then mounted on glass slides and stained.

- 7 -

Immunolocalisation of collagen type II, chondroitin 4 sulphate and chondroitin 6 sulphate. Dewaxed sections were chondroitinase digested (0.25 iu/ml) for one hour at 38°C to reveal the epitopes before immunolocalisation. Selected

5 primary monoclonal antibodies were used individually and a rhodamine conjugated anti-murine serum was applied to each section, after appropriate wash steps between stages. Non-immune mouse serum was applied as control to all immunolocalisations and pre-absorbed anti-collagen type II
10 monoclonal was used as an extra control for the localisation of collagen type II which is specific to cartilage.

Electron Microscopy. At each time interval, excess bone was removed from the femoral condyles before fine trimming to the area of defect repair, before fixation with 2.5%
15 glutaraldehyde in sodium cacodylate buffer at 4°C, for a minimum 48 hours. Specimens were post fixed in 1% osmium tetroxide for 2 hours before dehydration through a methanol series into propylene oxide and embedding in Spurr's resin.

The results observed were as follows:

20 Macroscopic findings. None of the rabbits died, nor was there any evidence of infection. The rabbits were housed in group pens which allowed freedom of movement i.e. running, jumping, standing on hind legs. The animals showed no sign of discomfort and all enjoyed full mobility.
25 In most rabbits the knee joints showed a white glistening cartilage-like tissue resembling the normal surrounding articular cartilage. There appeared to be a good overgrowth of cartilage over the polymer within the defect. In three rabbit knees the tissue covering was incomplete; histological
30 observations revealed that the polymer had been set above the level of the subchondral bone in the cartilage defect. Since cartilage cannot grow through the polymer, it is therefore important that the polymer is set at the right level to allow good resurfacing.

- 8 -

Two rabbits were kept for a longer study (eight months). The joints remained functional throughout the study period. The histology revealed that the new cartilage remained intact but the density of the matrix had still not achieved that of the original cartilage. There were still a mixed population of cells and areas of fibrous and chondrogenic regions. The subchondral bone had remodelled and in it the polymer became surrounded by very dense collagen.

Frozen sections. Cryostat sectioning allowed visualisation of the intact polymer-tissue interface, hence the extracellular matrix components of the tissue growing over the polymer three weeks after surgery were characterised. Histologically a variety of tissues were observed. Most prominent in the early stages was the observation of a highly cellular fibrous tissue. A thin layer of synovial appearance separated the new tissue covering the polymer from the intracondylar space. Bony spicules appeared to be associated with areas of new tissue immediately adjacent to the polymer surface. Above this interface the fibrous layer contained areas of rounded cells in a metachromatically stained matrix believed to be chondrogenic nodules.

Low temperature wax embedded tissue sections. Immunolocalisation of collagen type II within the cartilaginous nodules confirmed the chondrogenic phenotype of these areas of the tissue. Immunolocalisation studies also demonstrated an elaboration of chondroitin 4-sulphate and chondroitin 6-sulphate glycosaminoglycan side chains both in the fibrous tissue and in the regions of chondrogenic nodules. The varieties of cell phenotypes within the layer covering the polymer were shown histologically and by immunolocalisation of their matrix molecules during the first twelve weeks after implantation.

Transmission electron microscopy of the trans-polymer tissue layer after 8 months of implantation showed the rounded appearance of cells within a proteoglycan rich matrix,

- 9 -

indicating the chondrogenic nature of the tissue. The presence of chondron at the cartilage and bone interface was noted.

5 Growth hormone incorporation. It was shown that the cured polymer system was a good vehicle for the release of growth hormone. Morphological comparisons were made between the tissue covering the growth hormone and plain polymer.

Figures 2 to 6 illustrate the above findings as follows:

Figure 2

10 After 3 weeks of implantation a fibrous tissue layer (f) had grown over the polymer (P) surface. The polymer (P) had been inserted into a sub-chondral defect in the bone (B) below the level of the remaining cartilage (C).

Decalcified tissue embedded in wax. Section is stained with Methylene blue-Azur II.

15 Figure 3

20 After 6 weeks of implantation two zones of repair tissue were observed. Bony spicules (b) and nodules containing chondrocytes (arrowed) are seen in the zone immediately above the polymer (P) surface. Where the defect has been made in the cartilage (C) a tissue layer similar in appearance but less organised than normal cartilage (c) has formed above the bony zone. Original bone is denoted B, and the original cartilage is denoted C.

25 Decalcified tissue embedded in wax. Section is stained with Methylene blue-Azur II.

Figure 4

30 After 9 weeks of implantation there is more new bone (b) above the polymer (P) surface. There are nodules containing chondrocytes (arrow) in the bony layer. The new cartilage (c) is disorganised. Original bone is denoted B, and the original cartilage is denoted C.

Decalcified tissue embedded in wax. Section is stained with Methylene blue-Azur II.

- 10 -

Figure 5

By transmission electron microscopy clusters of chondrocytes are seen to be contained within a collagenous basket (co). These 5 are referred to as chondrons and are structures normally observed in the deep zones of mammalian cartilage. The normal extracellular matrix is denoted M.

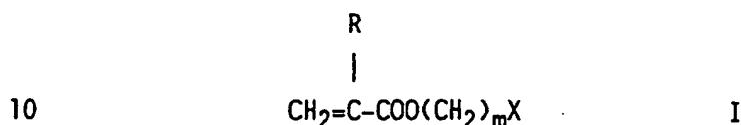
Figure 6

The cells within the chondron (Co) appear to be actively 10 synthesising cell products indicated by the enormous amount of endoplasmic reticulum (ER). The cell nucleus is denoted N and the normal extracellular matrix is denoted M.

- 11 -

CLAIMS

1. A monomer/polymer mixture for use in the preparation of a
curable composition for introduction to a site requiring tissue
repair in a human or animal body in order to promote said
5 tissue repair, the monomer component being selected from
monomeric esters of general formula I



where R is a hydrogen atom or a methyl group, m is 0, 1 or 2 and X is a 3 to 6 membered heterocyclic ring and the polymer component is selected from acrylate and methacrylate polymers and copolymers thereof.

2. A mixture according to Claim 1 wherein X in the monomer component of formula I is an oxygen containing heterocycle.
3. A mixture according to Claim 2 wherein the monomer component is tetrahydrofurfuryl methacrylate.
- 20 4. A mixture according to Claim 1, 2 or 3 wherein the polymer component is polyethylmethacrylate.
5. A mixture according to any one of the preceding claims for use in the preparation of a curable composition having a polymer to monomer ratio of 1:1 to 2:1 by weight.
- 25 6. A mixture according to any one of the preceding claims, for use in the preparation of a curable composition, further comprising one or more components selected from antibiotic and therapeutic agents, antifungal and antimicrobial agents, porosogens, protein carriers and cell growth stimulants.
- 30 7. A mixture according to Claim 6 wherein the, or one of the, additives is human growth hormone.
8. A mixture according to any one of the preceding claims for use in the preparation of a curable composition for introduction to a site requiring cartilage repair.

- 12 -

9. A process for the promotion of tissue repair comprising introducing to a site requiring tissue repair in a human or animal body a curable composition in accordance with any one of Claims 1 to 7 and causing or allowing the composition to cure 5 in contact with the site.
10. A process according to Claim 9 for the promotion of cartilage repair.
11. A process according to Claim 9 wherein the curable composition is introduced below the surface of the subchondral 10 bone.

1/6

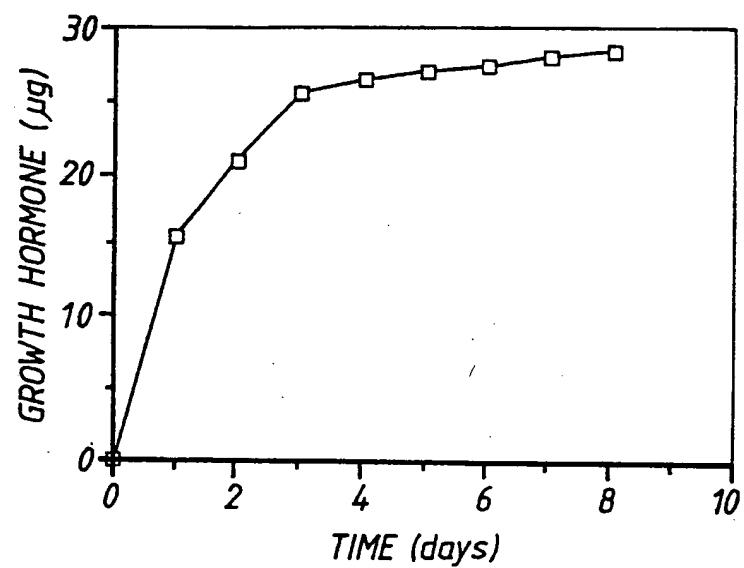


Fig. 1

2/6



Fig. 2

3/6

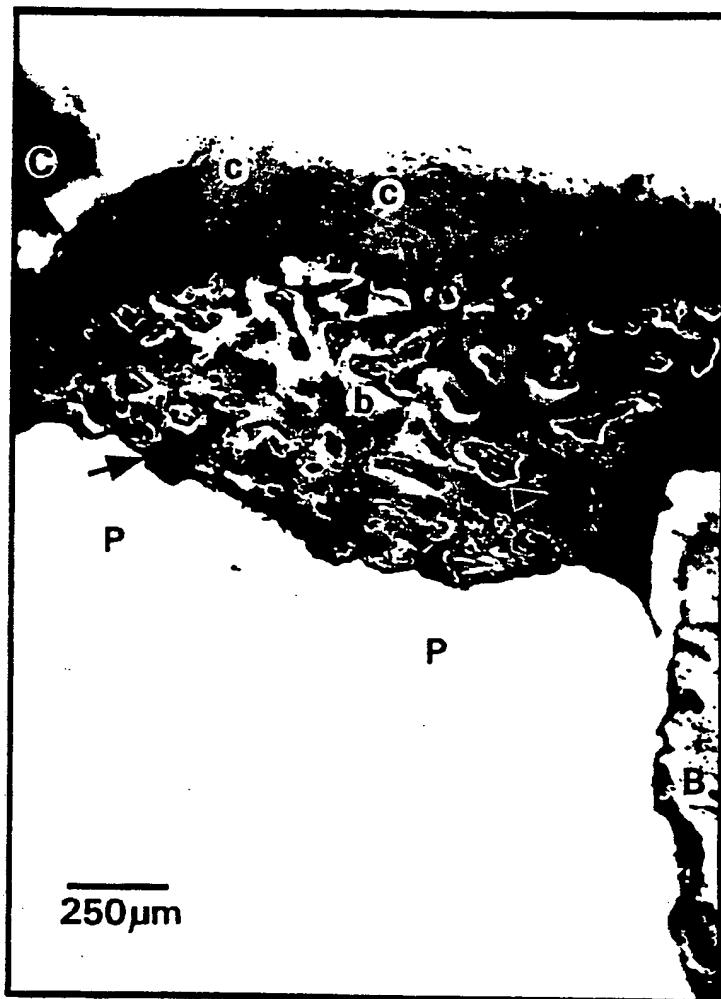


Fig. 3

4/6

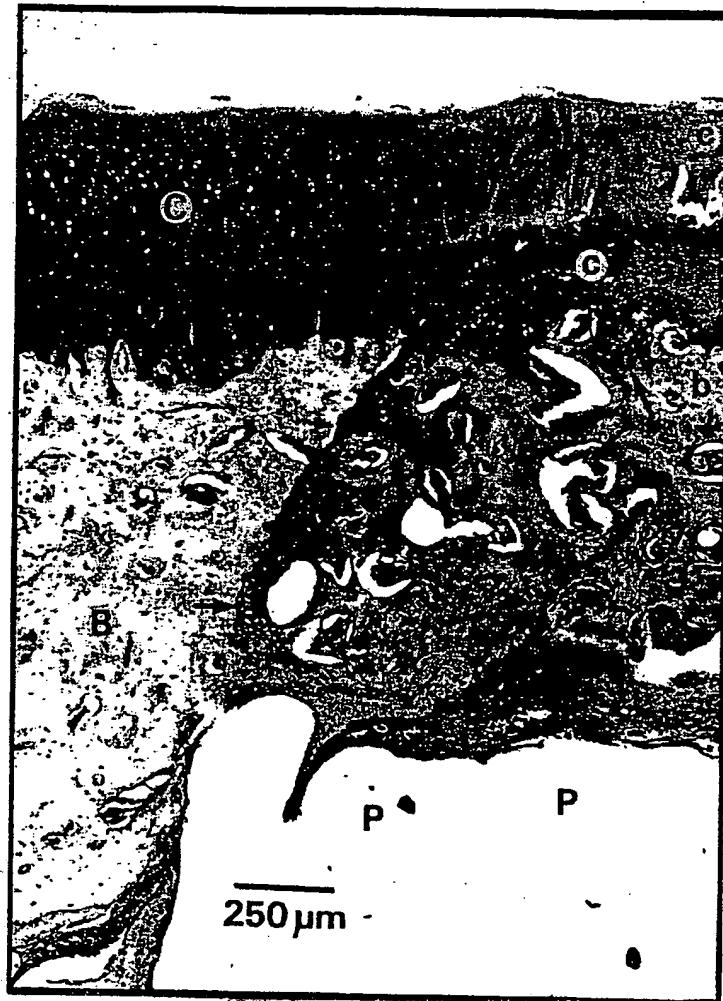


Fig. 4

5/6

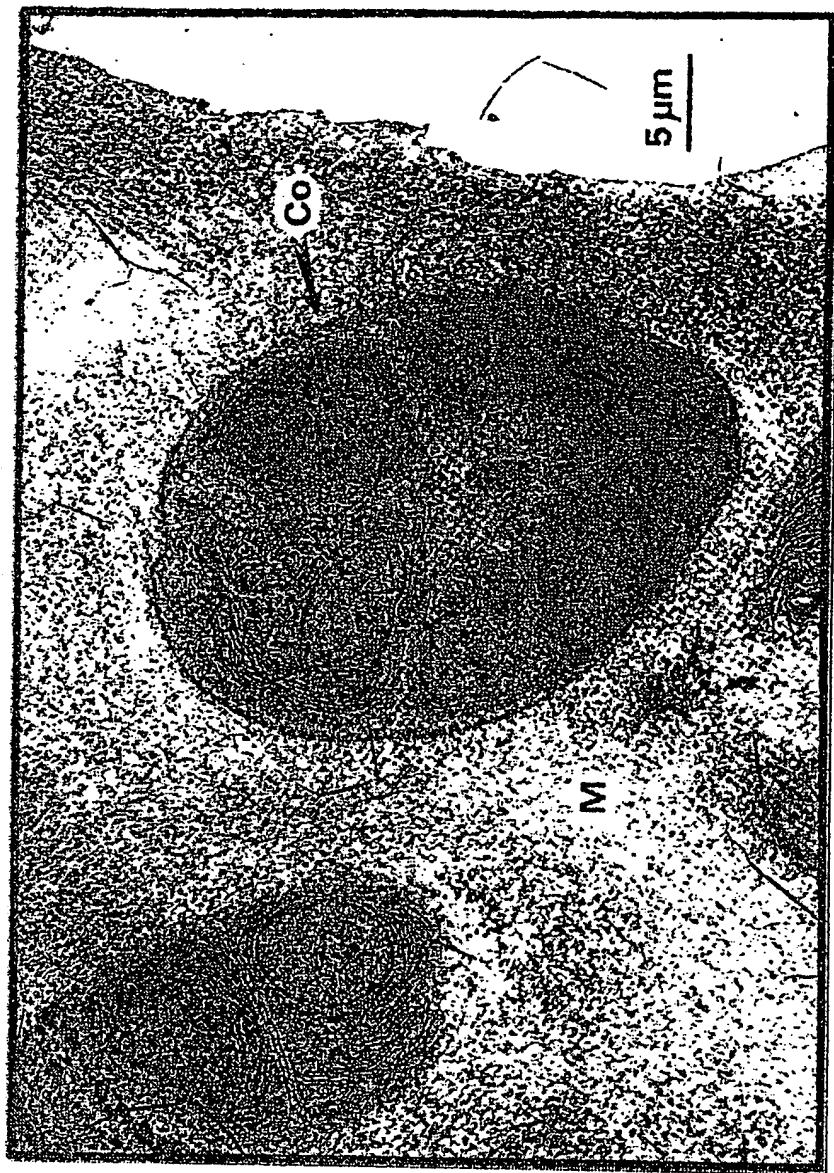


Fig. 5

6/6

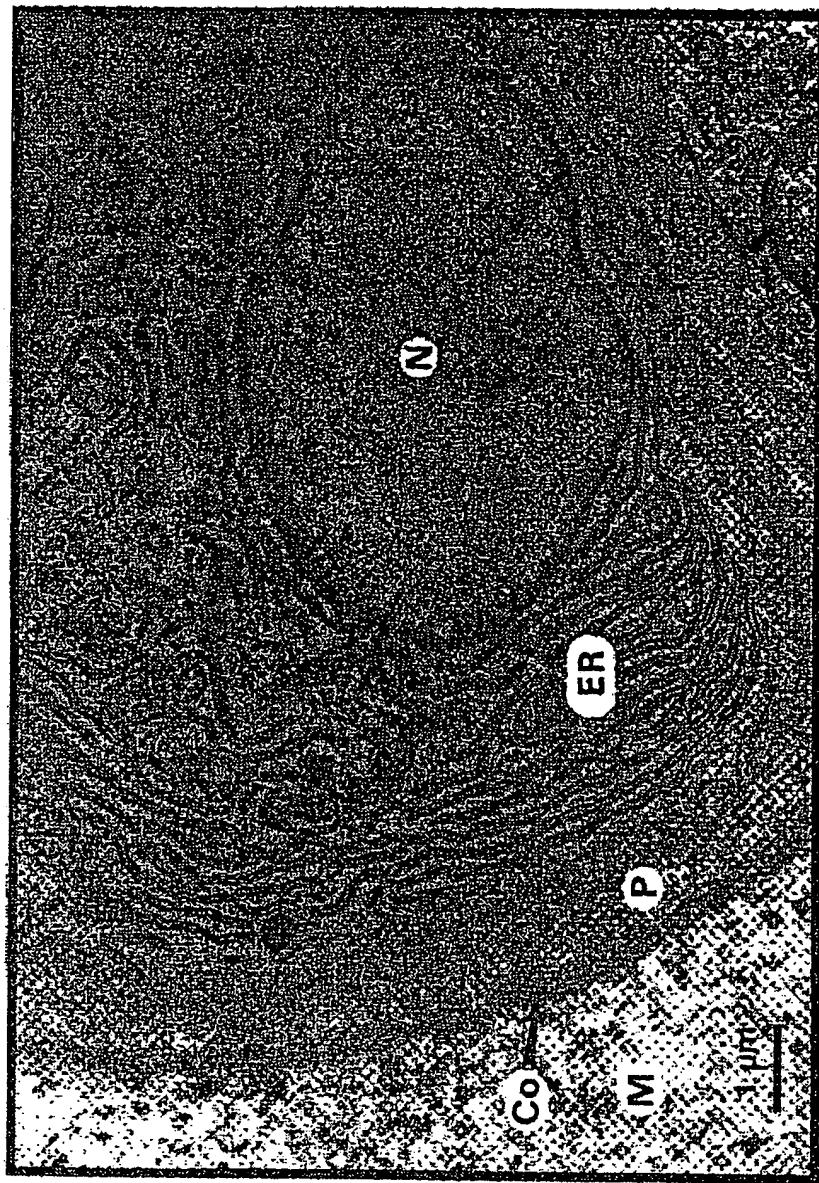


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 92/02128

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61L 27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61L C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | EP, A2, 0088845 (SECRETARY OF STATE FOR SOCIAL SERVICES IN HER BRITANNIC MAJESTY'S GOVERNMENT OF THE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND...), 21 Sept 1983 (21.09.83) | 1-5 |
| Y | -- | 6-7 |
| A | WO, A1, 8903695 (NORDISK GENTOFTE A/S), 5 May 1989 (05.05.89) | 1-5 |
| Y | -- | 6-7 |

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

11 February 1993

Date of mailing of the international search report

03 MAR 1993

Name and mailing address of the ISA/
 European Patent Office, P.B. 5818 Patentzaan 2
 NL-2280-HV Rijswijk
 Tel. (+31-70) 340-2040, Telex 31 651 epo nl.
 Fax (+31-70) 340-3016

Authorized officer

SOFIA NIKOLOPOULOU

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 92/02128

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| A | EP, A2, 0032249 (DEN-MAT, INC.), 22 July 1981 (22.07.81) --- | 1-11 |
| P,X | Chemical Abstracts, Volume 116, No 4, 27 January 1992 (27.01.92), (Columbus, Ohio, USA), Patel, M.P. et al, "Heterocyclic methacrylates for clinical applications. II. Room temperature polymerizing systems for potential clinical use", page 460, THE ABSTRACT No 28061h, Biomaterials 1991, 12 (7), 649-652 --- ----- | 1-2 |

SA: 5644

INTERNATIONAL SEARCH REPORT

Information on patent family members

08/01/93

International application No.

PCT/GB 92/02128

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|--|--|--|
| EP-A2- 0088845 | 21/09/83 | GB-A,B- | 2107341 | 27/04/83 |
| WO-A1- 8903695 | 05/05/89 | AU-A- EP-A- JP-T- | 2616088 0386056 3505406 | 23/05/89 12/09/90 28/11/91 |
| EP-A2- 0032249 | 22/07/81 | AT-E,T- AU-B- AU-A- CA-A- US-A- WO-A- | 6735 539337 6782781 1134532 4264489 8102022 | 15/04/84 20/09/84 07/08/81 26/10/82 28/04/81 23/07/81 |

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.